Predictors of human PBDE body burdens for a UK cohort

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Abstract

Human exposure to polybrominated diphenyl ethers (PBDEs) was investigated in a cohort of 20 UK adults along with their anthropometric covariates and relevant properties such as room surveys, lifestyle, diet and activity details. Selected PBDE congeners were measured in matched samples of indoor dust, (n=41), vehicles (n=8), duplicate diet (n=24), serum (n=24) and breast milk (n=6).

Combined exposure estimates via dust and diet revealed total PBDE intakes of 104 to 81,440 pg kg^{-1} bw d^{-1} for $\Sigma BDEs_{3\text{-}7}$ and 1,170 to 17,000 pg kg^{-1} bw d^{-1} for BDE-209. These adult intakes are well within health reference doses suggested by the European Food Safety Authority (EFSA) and the US EPA. For this cohort diet was the primary source of intake of $BDE_{3\text{-}7}$ congeners for the majority of the cohort, with dust the primary source of BDE-209. Primary sources of PBDE exposure vary between countries and regions with differing fire prevention regulations. Estimated infant exposures (ages 1.5 to 4.5 years) showed that BDE-99 intake for one of the households did not meet EFSA's recommended margin of exposure, a further two households were borderline for high level dust and diet intake.

Males and those having a lower body fat mass had higher serum BDE-153. Higher meat consumption was significantly correlated with higher $BDEs_{3\text{-}7}$ in serum. A reduction in dietary $BDEs_{3\text{-}7}$ would therefore result in the greatest reduction in BDE-99 exposure. Rooms containing PUF sofas or armchairs over 20 years old had higher $BDEs_{3\text{-}7}$ in their dust, and rooms with carpets or rugs of that age had higher dust BDE-209. Dusting rooms more frequently resulted in significantly lower concentrations of all major congeners in their dust. Correlation between BDE-209 body burden and dust or diet exposure was limited by its low bioaccessibiliy. Although vehicle dust contained the highest concentrations of $BDEs_{3\text{-}7}$ and BDE-209, serum $BDEs_{3\text{-}7}$ correlated most strongly with bedroom dust.

1 Introduction

UK residents are still exposed to a class of potentially harmful brominated flame retardants, polybrominated diphenyl ethers (PBDEs), even though European Union regulations restricting their manufacture, use and importation came into force in 2004 and 2008. Since the 1970s PBDEs have been incorporated into fabrics, foam cushioning and plastics used in everyday items such as vehicles, soft furnishings and electronics. PBDEs slow the rate of ignition and fire growth in petroleum based polymers and resins. PBDEs are not chemically bonded to these materials and are emitted into indoor dust and air through use and volatilisation (Rauert and Harrad, 2015; Sjödin et al., 2003). They can then move into the wider environment where they have been found in sewage sludge, soils and river and lake sediments (Allchin et al., 1999; De Boer et al., 2003; Eljarrat et al., 2008; Harrad et al., 2009). They are persistent organic pollutants as defined by the United Nations Environment Programme's Stockholm Convention and have an environmental half-life of several years. They can travel long distances in the atmosphere and are lipophilic, concentrating in animal and marine fats. These qualities and their wide usage have led them to permeate environments and food chains around the world (Fromme et al., 2016).

A recent systematic review of human health consequences of exposure to PBDEs concluded health effects may include thyroid disorders, reproductive health effects, and neurobehavioral and developmental disorders (Kim et al., 2014). Evidence of these effects has been seen in animal and *in vitro* research, where the mechanism appears to be altered hormone regulation (endocrine disruption) (Linares et al., 2015; Marchesini et al., 2008; Meerts et al., 2000; Viberg et al., 2006). Exposure during key developmental stages in infancy is most damaging as this is the time when altered hormone regulation will have the greatest impact. Recent estimates of the economic cost of just the intelligence quotient (IQ) points loss and intellectual disability due to PBDE exposure was $266 billion in the USA and $12·6 billion in the EU (Attina et al., 2016). These figures must be balanced against amounts saved due to fire prevention resulting from furnishing flammability standards e.g. £140 million annual savings in the UK estimated by prevention of death, injury and damage to property as a result of Furniture and Furnishings Fire Safety Regulations 1988 that require

use of flame retardant chemicals. (BIS, 2009). PBDEs were only one group of flame retardant chemicals from the several BFR groups commonly used to meet such regulations.

In 2004, use of two commercial PBDE products, Penta-BDE and Octa-BDE, were restricted within the EU (European Council Directive 2003/11/EC) and voluntarily phased out in the USA. In 2009, they were added to the Stockholm Convention list of POPs for elimination. Penta-BDE had been primarily used in polyurethane foam (PUF) in soft furnishings, vehicles and printed circuit boards, in greatest amounts in the USA. Furnishings could contain one to four percent Penta-BDE to comply with fire safety regulations (Hammel et al., 2017). The Octa-BDE commercial product has been produced and used less widely than Penta-BDE. Its major use has been in acrylonitrile-butadiene-styrene (ABS) plastics, such as electronics and resin casings of office equipment. The Deca-BDE commercial product has been added to furnishing textiles, and in high impact polystyrene (HIPS) for cables, sockets, mobile phones, fridges and TV housings.

Concentrations of BDE-209 are higher in UK indoor dusts than in dusts from mainland Europe (Frederiksen et al., 2009; Harrad et al., 2008b) as a result of the UK's more stringent fire safety regulations (Furniture and Furnishings Fire Safety Regulations 1988/1989, 1993 and 2010). Deca-BDE has been restricted from use in electrical and electronic equipment in the EU since 2008 and was added to Annex A of the Stockholm Convention list of POPs in 2017. Both diet and contact with indoor dust constitute important exposure pathways for PBDEs (Abdallah and Harrad, 2014). Foods from higher up the food chain, of animal origin, with a higher fat content (i.e. fish), meat and dairy have higher PBDE concentrations (EFSA, 2011). PBDEs will be circulating in our food chains for many years to come (Harrad and Diamond, 2006), and will be re-circulated back into homes as a result of plastics recycling (Samsonek and Puype, 2013) .

Whether dust or diet is the primary exposure source for an individual depends on a number of factors; loading of PBDE in dust or food items and the amounts ingested, whether and when PBDE technical products have been phased out in that country and on the age of the individual (Bramwell et al., 2016a). PBDE intake via ingestion and inhalation of dust is the major exposure route for young children in the USA that have frequent hand to mouth behaviours and spend lots of time on floors and carpets (Stapleton et al., 2012). Foetal exposure in the womb and transfer of PBDEs from mother to child during breastfeeding are

key exposures for children during important developmental periods. For countries outside of the US and Canada, the largest contribution to tri-hepta BDE body burden is thought to be from diet, especially in regions where Penta-BDE use has been restricted for longer. Dust is likely to be most important contributor to exposure to higher brominated congeners in all regions (Sahlström et al., 2015).

The aim of this study was to determine the major dust and diet sources of PBDEs for a north east England cohort and to consider any potential health risks. The five specific objectives were: (a) to measure PBDE concentrations in dust from homes, work places and vehicles, (b) to calculate relative intake of PBDE via dust in the microenvironments, (c) to evaluate the relative importance of PBDE exposure via indoor dust versus dietary PBDE exposure, (d) to compare intake estimates with reference health values, (e) to investigate relationships between matched environmental and biomonitoring data, and (f) to determine the most effective means of reducing PBDE exposure for the cohort.

2 Materials and Methods

We used a cross sectional and purposive sampling strategy to provide a snap shot of PBDE exposures and body burdens for individuals with expected high, average and low exposures. By comparing individuals with expected divergent exposures, we aimed to reveal the factors influencing body burdens.

2.1 Volunteer recruitment

We targeted individuals with a range of occupations and diets; such as workers in electronics, soft furnishings, transport, office workers, outdoor workers, oily fish eaters, omnivores and vegetarians. In 2010/11, following ethical approval for the study, volunteers over 18 years of age and with six months or more of domestic and occupational stability were recruited via local authorities, universities, businesses, hospitals, playgroups and breast-feeding groups. A short pre-screening questionnaire was used to identify volunteers that could provide the optimum range of exposures. 79 couples completed the pre-screening questionnaires, 10 couples were invited, and agreed, to participate in the full

study week. Further description of the cohort is provided in the Supplementary Information. Volunteers gave written informed consent prior to participation.

2.2 Timing of sample collection

Participants undertook a 'sampling week' during which they completed an exposure and food frequency questionnaire (FFQ), food- and activity-diaries, room surveys including contents, usage and cleaning information and they were asked not to vacuum or dust their home. We adapted the validated WHO-IARC EPIC semi-quantitative dietary questionnaire for the study. On the seventh day of their sampling week, participants collected their duplicate diet samples (DD), and the researcher visited that evening to collect the DD samples, home and vehicle dust samples, questionnaires and surveys. The participants then fasted until their blood sample collection appointment the following morning where anthropometric measurements were also taken. Two couples repeated the full sampling week, with sampling points 6.5 and 7.5 months apart. This provided a longitudinal dimension to the study and an element of validation. All sampling weeks took place between April 1st 2011 and 28th February 2012.

2.3 Serum, breast milk and duplicate diets

Study participants collected an equal amount of whatever food they ate throughout the day in a contaminant free (verified by tests carried out prior to sampling) lidded polypropylene container for the 24 hour duplicate diet collection. The next day they provided a fasted 60 ml blood sample at the Clinical Research Facility of the Royal Victoria Infirmary in Newcastle. 150 ml breastmilk samples were collected by either pump or manual expression up to 12 h before and 24 h after provision of the blood sample and kept in pre-cleaned Nalgene containers. Samples were stored at -18^{o}C until transfer to the laboratory for analysis. Details of the serum, human milk and duplicate diet sample collection and analysis have been published previously (Bramwell et al., 2014; Bramwell et al., 2017).

2.4 Dust samples

Participants were requested not to vacuum or dust their home or vehicle during the sampling week. Dust samples from main living areas (n=11), bedrooms (n=12), and vehicles

(n=8) were collected by a researcher following a standard sampling protocol to allow direct comparison with previous studies (Abdallah and Harrad, 2009; Coakley et al., 2013; Harrad et al., 2008a; Harrad et al., 2008b). Samples from workplaces (n=10) were collected during the sampling week at the participants' (and their employers') convenience. Dust samples were extracted and analysed at the University of Birmingham, UK, using previously published methods for preparation, extraction, clean up, analysis and quality control (Abdallah et al., 2009; Harrad et al., 2008a; Harrad et al., 2008b). Further details of the dust sample collection, preparation, extraction and analysis are provided in the Supplementary Information.

2.5 QA/QC

For the analysis of serum, breast milk and duplicate diet samples, the performance characteristics of the methodology, including quality assurance parameters such as limits of detection (LODs), precision, linear range of measurement, recoveries etc. are included in the previous reports (Fernandes et al., 2008; Fernandes, 2004). Further confidence in the data is provided by regular and successful participation in laboratory proficiency testing and inter-comparison schemes such as POPs in Food 2011 and 2012. PBDEs with IUPAC numbers 17, 28, 47, 49, 66, 71, 77, 85, 99, 100, 119, 126, 138, 153, 154, 183 and 209 were measured. The congeners selected for analysis are those for which reference standards are available. Typical LODs were 1 to 20 ng kg^{-1} lipid for PBDEs.

For the dust sample analysis the average blank (including field blanks) plus 3 standard deviations was used for the limit of detection giving an average 0.7 ng g^{-1} for $BDEs_{3\text{-}7}$ (range 0.2-1.7) and 52 ng g^{-1} for BDE-209. The PBDE ^{13}C labelled internal standard recoveries were: ^{13}C-BDE 47 = 69 ± 20%, ^{13}C-BDE 99 = 70 ± 20%, ^{13}C-BDE 153 = 69 ± 20% and ^{13}C-BDE 209 = 17 ± 6%. The low recovery for BDE-209 indicates uncertainties in its measurement which are presented here with that caveat. Measurement of SRM NIST 2585 had range 78% (BDE-47) to 122% (BDE-49) and mean 100% of the certified contents.

2.6 Exposure Assessment

Concentrations of the PBDEs detected in milk and serum samples were lipid-adjusted to allow comparison with the literature. PBDE intake for the 24 hrs of the duplicate diet collection was measured using whole weight duplicate diet PBDE concentrations multiplied

by the mass of DD collected and divided by the weight of the participant to give pg kg^{-1} body weight day^{-1}.

PBDE intakes via dust were estimated by combining measured dust PBDE concentrations with occupation time for individual's various microenvironments (taken from their activity diary) using both average (20 mg/ day) and high (50 mg/day) adult dust intake rates average and high adult dust ingestion as estimated by Jones-Otazo et al. (2005). Although dust ingestion rates may differ between microenvironments and activities (as well as individuals), for the purpose of this study, we have assumed that that dust ingestion occurred pro-rata to the proportion of time spent in each microenvironment during the study week. This was considered the only practical approach in the absence of data to confirm any differences (Abdallah and Harrad, 2009). For time periods when participants were in their home but not in one of the microenvironments measured, the median of their home dust PBDE concentration was used. For time periods when they were in an indoor environment but not in their own home the median of all dusts collected for the study was used. Time spent outside was not assigned a PBDE concentration. Intake rates via dust were divided by the participant's weight to give pg PBDE intake kg^{-1} body weight day^{-1}.

PBDE intakes for average and high dust intake scenarios: average 20 mg d^{-1}, high 50 mg d^{-1} (Jones-Otazo et al., 2005) and diet intakes determined from the 24 h duplicate diet concentrations were added together for comparison with the European Food Safety Authority's (EFSA) chronic human daily dietary intake estimations to determine the margins of exposure (MOEs). As PBDE exposure during infancy is considered to present a greater risk to health than that for adults, estimated average and high exposure scenarios for infants aged 1.5 to 4.5 years old were developed as well. Daily average (50 mg d^{-1}) and high (200 mg d^{-1}) dust intake estimations (Jones-Otazo et al., 2005) per kg body weight were extrapolated from individual adult intake values determined for the study. These were added to average and high dietary PBDE intake estimations from the UK total diet study (TDS) (2012) data for infants aged 1.5 to 4.5 years old. Risk assessment for infants from PBDE in breast milks collected for the study has been previously reported (Bramwell et al., 2014).

2.7 Data Analysis

Associations between PBDE concentrations and intakes and potential predictors were explored with scatter plots, box plots and correlations using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp, Minitab 17 and Excel (Microsoft Office 2013). The distribution of PBDEs in the different matrices was assessed using Shapiro–Wilk statistic. As the majority of distributions were not normal, non-parametric Spearman's ranking correlation coefficients were determined. The criteria of $\alpha = 0.05$ for statistical significance was used. A one sample t test was used to compare PBDE intake of omnivorous participants as determined by duplicate diet collection and similar data collected by Harrad et al. (2004) to investigate any temporal trend in dietary exposure. Statistical analyses were mostly descriptive and correlations do not have sufficient sample numbers to be robust. Details of further statistical analyses of room survey data are presented in the Supplementary Information. Where measurements were below limits of detection (LOD) values of LOD*0.5 have been assumed (median bound). $\sum BDEs_{3\text{-}7}$ was calculated as the sum of all BDE congeners measured except for BDE-209.

2.8 Human health risk characterisation

Potential health risks were calculated from the sum of dust and dietary intake of PBDEs using the margin of exposure (MOE) approach as applied by the European Food Safety Authority (EFSA) for dietary exposure health risk assessment. The MOE is the ratio of the dose at which a small but measureable adverse effect has been reported versus the level of exposure of the population under current consideration. The EFSA Panel on Contaminants in the food chain (EFSA, 2011) identified effects on neurodevelopment as the critical endpoint using $BMDL_{10}$ for neurobehavioural effects in mice induced during a relevant period for brain development. Chronic human intakes, associated with body burdens at the $BMDL_{10}$ for BDEs-47, -99, -153 and -209, were estimated to be 172, 4.2, 9.6 and 1,700,000 ng kg^{-1} bw day^{-1} respectively. For PBDEs, EFSA consider that an MOE ratio above 2.5 indicates that a health concern is unlikely, with risk decreasing as the MOE increases (EFSA, 2011). It should be noted that although human intakes of concern are presented as daily doses these represent chronic intake and as such would be better represented as weekly or monthly intakes as daily intakes can be exceeded on occasion without concern as long as other days have lower exposures.

3 Results and Discussion

Our cohort consisted of 10 male-female cohabiting couples living in northeast England in 2011/12. All participants completed full sample and data set collection. Participants were recruited from as wide a pool of socio-economic class, occupation, diet and location as possible, however, the small number of participants and the focus on breastfeeding mothers means that results are not representative of all UK residents' exposures. The benefit of the small cohort was that detailed information could be collected for each individual allowing the investigation to include almost all contributing factors in PBDE exposure known at the time. Further details of occupations, diets, parity, breastfeeding and other lifestyle and anthropometric factors are presented in Supplementary Information. Previously published serum, breastmilk, and duplicate diet concentrations (Bramwell et al., 2014; Bramwell et al., 2016b) have been further examined in this investigation, along with new matched dust concentrations, diet and dust intake estimations and exposure and food frequency questionnaire, seven day food and activity diary and room survey information in order to provide as complete a picture of participants' PBDE exposures as possible.

3.1 Dust PBDE concentrations

Dust samples were collected from 40 micro-environments frequently used by the study participants. Main living areas (n=10), bedrooms (n=12) and home offices (n=2) were sampled. Workplaces were sampled if access was granted by employers (n=8). None of the domestic samples were from open plan homes. Four of the workplace samples were from open plan indoor spaces. Vehicles were sampled if participants regularly spent more than five hours each week in them (n=8). We measured PBDEs in dust from all of the microenvironments sampled. Individual concentrations for all PBDEs in each dust sample are presented in Supplementary Information Tables SI 1-4 and summaries of the dust concentrations in different rooms are presented in Table 1. Median dust $\sum BDEs_{3\text{-}7}$ concentrations were highest in vehicles (179 ng g^{-1}) followed by living rooms, bedrooms then workplaces (137, 102 and 84 ng g^{-1} respectively). Median BDE-209 concentrations in dust were also highest in vehicles (19,000 ng g^{-1}) then bedrooms, living rooms and workplaces (3,530, 2,960, and 2,300 ng g^{-1} respectively). The highest concentration of

263∑BDEs$_{3\text{-}7}$ was measured in a bedroom (7,320 ng g^{-1} dust), the highest BDE-183 in the rear of
264a work van (367 ng g^{-1}) and the highest BDE-209 in a car (137,000 ng g^{-1}). Summaries of dust
265PBDE concentrations in the different microenvironments are compared with previous UK
266and international data in Table 2. Measurements in this study were in keeping with
267previously published UK data (Harrad et al., 2008a; Harrad et al., 2008b; Pless-Mulloli et al.,
2682006; Sjödin et al., 2008) and in agreement with the theory that BDE-209 usage was greater
269in the UK (Fromme et al., 2016; Harrad, 2015). Results were directly comparable to studies
270by Harrad et al. (2008a; 2008b) as we used the same sampling protocol, sampling
271equipment and laboratory techniques.

272We compared room survey information such as counts and age of soft furnishings and
273electronics and room cleaning frequencies with the concentrations of PBDEs in each room.
274Details from individual room surveys are provided in Supplementary Information Table SI5.
275We did not find that simple counts of soft furnishings or electronics were good predictors of
276high or low PBDE loading. The clearest association between room contents and PBDE
277concentrations in dust were for BDE-209 if the room contained a carpet or rugs over 20
278years of age (see Supplementary Information Figure 2) . Counts of large PUF items over 20
279years old or office chairs from the USA (adhering to Californian state fire retardancy
280regulations TB117) correlated significantly with concentrations of Penta mix BDEs only, BDE-
28147 (r=0.37, p=0.036), -99 (r=0.35, p=0.047) and ∑BDE$_{3\text{-}7}$ (r=0.37, p=0.039). Higher dusting
282frequency demonstrated the greatest correlation with lower dust PBDE concentrations, with
283BDEs-47, -99, -153, -154 and -209 all with correlation significant at the 0.01 level and BDE-
284100 with correlation significant at the 0.05 level. Table SI 6 in the Supplementary
285Information contains further correlation data. Discussion of apparent differences between
286repeat sampling weeks' dust data is provided as Supplementary Information.

287We found that concentrations of ∑Penta product BDEs in the bedroom were significantly
288correlated with those in all other environments measured; living rooms (r=0.43, p=0.05),
289workplaces (r=0.71, p=0.05) and vehicles (r=0.90, p=0.02). Concentrations of ∑Penta product
290BDEs in living room dusts correlated strongly with those in workplaces (r=0.90, p=0.01) but
291not vehicles (r=0.30, p=0.60). A larger data set may have revealed alternative findings,
292particularly for workplaces and vehicles. We suggest that dust particles may briefly adhere
293to and then be shaken from skin, hair, clothing and footwear causing distribution among key

environments used by participants. Further correlation data is provided in Supplementary Information Table SI13.

3.2 Intake of PBDEs via dust

The ranges of average (20 mg dust ingested d^{-1}) and high (50 mg dust ingested d^{-1}) PBDE intakes via dust for our study participants was 13.8-1,010 and 35-2,520 pg kg^{-1} bw day^{-1} for $\sum BDEs_{3-7}$, with 281 to 15,900 and 702 to 39,600 pg kg^{-1} bw day^{-1} for BDE-209 via dust. Our $\sum BDEs_{3-7}$ estimates were similar to previous UK and German $\sum BDEs_{3-7}$ intake estimates (Fromme et al., 2009; Harrad et al., 2008a) and an order of magnitude lower than those in the USA (Harrad et al., 2008b). In contrast, our BDE-209 intakes from dust were similar to those of the USA (Harrad et al., 2008b) and an order of magnitude higher than Belgian and German estimates (Fromme et al., 2009; Roosens et al., 2009) (see Supplementary Information Table 6). The wide range of intakes reflected the diverse PBDE loadings measured in microenvironment dusts. For this cohort, the influence of specific items in specific microenvironments could be reasonably speculated on a case by case basis. However, although we expected our participant with occupational PUF and furnishing fabric exposure to have a raised PBDE body burden, their fastidious cleaning habits appear to have reduced their exposure.

The greatest proportion of the estimated dust intake for $\sum BDEs_{3-7}$, BDE-183 and BDE-209 took place in the bedroom (means 43%, 38% and 33% respectively) due to the greater amount of time spent in bedrooms. Workplaces and living rooms were the second most important microenvironments for $\sum BDEs_{3-7}$ exposure (mean 19%, 13%) and BDE-183 (20%, 21%). Vehicles were the second most important microenvironment for BDE-209 intake (20%). The relative proportions of PBDE intakes in different microenvironments for individual participants is illustrated in Figure 1. Our finding that the greater proportion of exposure to all congeners occurs in the bedroom is in keeping with our finding of an association between bedroom dust and serum concentrations of the PBDE congeners found in the commercial Penta-BDE products (BDE-47, -99, -100, -153) ($r=0.42$, $p=0.04$), an association that has also been reported elsewhere (Ali et al., 2014; Coakley et al., 2013; Watkins et al., 2012). Relationships between PBDE in dust and body burdens

We compared PBDE concentrations in dust in the different indoor environments with their matched PBDE body burdens. Significant associations were noted between Penta-mix BDEs in bedroom dust and serum (r=0.45, p=0.04). BDE-153 in bedroom dust was significantly associated with BDEs-47 (r=0.45, p=0.03), -99 (r=0.45, p=0.03), -209 (r=0.41, p=0.05) and $\sum BDEs_{3\text{-}7}$ (r=0.45, p=0.03) in serum. BDE-153 in serum was associated but not significantly with BDEs-153 (0.39, 0.06) and $\sum BDEs_{3\text{-}7}$ (0.39, 0.06) in bedroom dust. BDE-47 was associated but not significantly in living room dust and breast milk (0.77, 0.07). BDE-209 was significantly correlated in serum and workplace dusts (0.72, 0.02) however this was strongly influenced by one data point. Also correlated but not significantly in workplace dusts were BDEs-47 (0.57, 0.07) and -99 (0.53, 0.09). Table SI 7 in Supplementary Information provides further dust and body burden correlation data. No significant correlations were found between vehicle dust and serum despite vehicles having the highest PBDE concentrations in their dust, possibly due to participants spending less time in their cars than in other environments measured. The associations between bedroom dust and serum might be expected due to participants spending the greatest proportion of their day in this room, similarly for associations with workplace dust and serum.

3.3 Dietary intake of PBDEs

We estimated participants' PBDE intake from diet using three different methods, (i) a 24 hour duplicate diet sample collected the day before taking serum and milk samples, (ii) a seven day food diary completed the seven days prior to serum and milk sampling and (iii) a food frequency questionnaire (FFQ) to represent longer term eating habits. Concentrations of PBDEs in the 24 hour duplicate diet samples summarised in Table 1. $BDEs_{3\text{-}7}$ were measurable in all of the duplicate diet samples and BDE-209 in 79% of them. 24 hour duplicate diet PBDE concentrations were converted to daily dietary intake estimates which ranged from 82 – 1,320 pg kg^{-1} bw for $\sum BDEs_{3\text{-}7}$ and <0.8- 1,860 pg kg^{-1} bw for BDE-209. BDE-209 made up a median of 73% of the total PBDE exposure from diet. Estimates of individuals' PBDE intake via diet are provided in Supplementary Information Table SI 11. The mean intake estimates of BDEs-47, -99, -100, -153 and -154 for the omnivores in this study were significantly lower than those measured by Harrad et al. (2004) for duplicate diet samples collected in the West Midlands of the UK in 2002 (p=0.01). The 2002 lower bound

mean intakes were within the maximum intakes estimated by this study for BDEs -47, -100, -153 and -154 and upper bound intakes for BDEs -47, -100, and -154. These findings indicate a reduction in dietary exposure during the 10 years between the two studies, with the greatest reductions being for BDE-99 then BDE-153.

Meat, fish and dairy portion consumption estimates compared well between the FFQ and seven day food diaries. Meat portions consumed per week ranged from none to 14 or 15 (FFQ and diary respectively), with median 6.3 or 8 portions. Fish and seafood portions consumed per week ranged from none to 3.5 (maximum for both FFQ and diary), with median 1.8 or 2 portions. Dairy portions consumed per week ranged from none to 25 or 18 (FFQ and diary respectively), with median 8.0 or 8.5 portions. A summary of selected information from the FFQ, diary and 24h duplicate diet is presented in Table 3.

3.4 Relationships between PBDE in diet, serum and breastmilk

We compared PBDE body burdens with concentrations in the duplicate diet finding a significant association for $\sum BDEs_{3\text{-}7}$ in both ($r=0.41$, $p=0.05$). Serum samples were collected from fasted participants in order for the serum sample to represent the participants' background PBDE body burden without influence from recently consumed food. Breastmilk samples were not necessarily collected in a fasted state. The complex relationship between historic PBDE deposits in adipose tissue, recent diet, serum and breastmilk is beyond the scope of this paper. We found limited correlation between congeners in serum and breastmilk (see Supplementary Information Table SI 8), possibly the result of transfer of PBDEs from serum to milk varying between different congeners. Mean serum/milk ratios generally increased with molecular size and hydrophobicity, e.g. 1.3, 3.1 and 6.0 for BDEs-47, -99 and -209. This pattern was in keeping with findings of a 2012 review of PBDE in matched serum and breastmilk samples (Mannetje et al., 2012). BDE-153 in the body appears to follow a different pattern with a serum/milk ratio of 0.4, i.e. more in milk than serum.

We found that the number of meat portions consumed in the week prior to sampling had significant positive correlations with BDEs-99 (r=0.46, p=0.01) -153 (r=0.44, p=0.03) and $\sum BDEs_{3\text{-}7}$ (r=0.43, p=0.04) in serum. Further correlation data between dietary information is provided in Supplementary Information Table SI9. The UK FSA 2006 TDS found meat products (followed by fish) to contribute most to the PBDE intake of the general UK population (EFSA, 2011; FSA, 2006). For participants in this study, meat portions consumed exceeded fish portions. Our earlier review of associations between PBDE body burden, dust and diet (Bramwell et al., 2016a) also found eating meat to be the most frequently reported association (eating dairy and fish were next). Similarly, a nationwide study in the USA found vegetarians to have 23% lower, and heavy red meat consumers to have 18% higher total PBDEs in serum than omnivores (Fraser et al., 2009).

3.5 Anthropometric and questionnaire covariates of PBDE body burden

As well as participants' height, weight and body fat mass measurements, information on travel habits, hand to mouth behaviours, parity, numbers of household members, hobbies and occupations was also collected to look for indicators of higher serum and breast milk PBDE concentrations. These associations are presented in Supplementary Information Table SI10. We found serum BDE-153 concentrations to be significantly associated with sex (r= -0.60, p=0.01), percentage of body fat mass (r=-0.49, p=0.02), parity in women (r=-0.57, p=0.05) and working with electronics (r=0.59, p=0.01). Males generally had higher BDE-153 in serum than females, in keeping with the findings of a recent Swedish study of 170 adults (Bjermo et al., 2017) and a nationwide study in the USA that found males generally had higher $BDE_{3\text{-}7}$ body burdens (Fraser et al., 2009). We hypothesise there may be two factors influencing the higher serum concentrations of males in this study, (i) men generally had lower BMI values; seven of the females had recently been pregnant which would increase their BMI and (ii) 9 of the 10 female participants in the study had undergone some depuration effect during pregnancy and breast feeding which their male partners had not. In a study of the breastmilk of 83 women at three and 12 months postpartum, BDE-153 showed a significant increase over time (Daniels et al., 2010) suggesting that BDE-153 present in adipose fat compartments from historic exposures may have been mobilised during the nursing period. Storage of BDE-153 in fat compartments in the body has been

suggested as the reason for dilution in the serum of people with higher BMI (Cequier et al., 2015; Fraser et al., 2009). Why these findings for BDE-153 are not consistent with findings for other congeners is not clear but it may be linked to its longer human half-life (Geyer et al., 2004).

3.6 Was diet or dust the major source of PBDE exposure for this cohort?

Diet was the major source of $\sum BDEs_{3\text{-}7}$ for this cohort making up a median of 85% of the total intake when using duplicate diet data with the average dust ingestion estimate of 20 mg d^{-1}. This was a somewhat lower proportion than comparable previous studies estimates of 95% (UK), 96% (Belgium) and 97%, (Germany) (Abdallah and Harrad, 2014; Fromme et al., 2009; Roosens et al., 2009) due to our higher median $\sum BDEs_{3\text{-}7}$ dust concentration and the notably higher concentration of $\sum BDEs_{3\text{-}7}$ in the German duplicate diets (see Table SI 6). We did not include estimates of intake of PBDEs from indoor air in our totals. Previous studies have found PBDE intake from air to constitute <1% of total PBDE intake (Fromme et al., 2009) and a maximum of 2% (Abdallah and Harrad, 2014).

Considering only a cohort's average intake hides the substantial variation between individuals and their exposure sources - something this study has been able to demonstrate clearly (see Figure 2 and Supplementary Information Table SI 6). An individual's total PBDE intake is a combination of dust concentrations in different environments, time spent in them and dietary habits. For example, the proportion of $\sum BDEs_{3\text{-}7}$ BDE intake provided by dust for an average dust intake rate had a median 4% but ranged between 0.7% (8M) and 32% (5F). Both these participants lived rurally, the former on a smallholding, the other on a farm. 8M spent the most time outdoors (almost 9 hours each day), had a low Penta-BDE loading in their bedroom dust and, despite a generally home-grown and organic diet, a duplicate diet intake in the 3rd quartile. 5F's relatively high dust intake (32% using average dust intake and 54% using high dust intake rates) was due to having the room (bedroom) with the highest $\sum BDEs_{3\text{-}7}$ concentrations measured in the study. Although 5F consumed a vegetarian diet their dietary $\sum BDEs_{3\text{-}7}$ intake was in the top quartile.

Dust was the greatest source of BDE-209 for our entire cohort, with median intakes making up 75% and 88% of the total BDE-209 intake for average and high dust intake rates

respectively, lower than previous UK estimates of 94% and 99% (Abdallah and Harrad, 2014; Harrad, 2010) possibly due to declining use of Deca-BDE product and differences between cohorts in the different studies. Individual participants' proportion of total BDE-209 intake provided by dust for average dust intake rate ranged from 14% (8M) to 100% (1Fii and 1Mii). Participant 10M had a significantly greater BDE-209 concentration than their partner possibly a reflection of the relatively high amount of time spent in their vehicle (23% of their time) and BDE-209 concentration in their car (30,338 ng/g).

We found the range of individuals' intakes of $\sum BDEs_{3\text{-}7}$ from dust to be five times greater than their intakes from diet. The highest total intake (using average dust intake scenario) was 16 times greater than the lowest reported intake. Our data agrees with previous hypotheses that the wide range in PBDE concentrations in room dusts (compared with the range seen in diets) may be the reason some individuals have significantly higher internal dose (Harrad et al., 2008b; Petreas et al., 2003; Thomas et al., 2006; Wu et al., 2007). Dust generation, dust ingestion rates, and cleaning frequencies (both microenvironments and hand washing) may also be influential.

Our study corroborates previous studies findings that average PBDE intakes in the UK are broadly similar to those in mainland Europe, where meat is the major source of Penta-BDEs for the average person but dust is the major source of BDE-209 (Bramwell et al., 2016a; Harrad et al., 2008b). For infants, the average contribution to total intakes from diet were >90% for $\sum BDEs_{3\text{-}7}$ and 69% for BDE-209. At the high dust ingestion rate this decreased to 35-50% for $\sum BDEs_{3\text{-}7}$ and 88% for BDE-209. These figures indicate similar proportional intake for infants from diet to our adults, although with considerably higher amounts ingested per kg body weight (see Table 3).

3.7 Study Limitations

This study involved a relatively small cohort of 20 individuals (10 UK couples). The study philosophy concentrated more on the details and habits of the volunteers in order to understand their individual exposures. The volume of usage of PBDE mixtures such as PentaBDE, the timelines of product introduction and restriction, either voluntary or regulation enforced, and the type of usage, are all variables in general population exposure. For example, a far greater volume of the PentaBDE mixture was used in the USA and Canada compared to Europe and this is reflected in the relatively higher concentrations of related congeners measured in serum, and in house dust levels from North

America. Also, where we found diet to be the most important exposure pathway for Penta mix BDEs, studies such as (Lorber, 2008) have shown that dust is a major pathway for PentaBDE in North American populations. When personal details and habits are considered, the exposure assessment is even more unique. Thus, the finding of this study are not intended to be representative of the UK as a whole, or even less, other regions of the world.

3.8 Risk characterisation

The most relevant congener from a health risk perspective is BDE-99 but there is no agreement on a safe intake. The US-EPA suggests a reference dose 100 ng/kg bw/day (US-EPA, 2006) whereas the more recent EFSA suggested health reference value is 4.2 ng/kg bw/day with an MOE of 2.5 (EFSA, 2011). We investigated potential health risk from our estimated PBDE intakes by comparing them with both these reference values (see Table 4 and Table SI12). The combined uncertainties from household types, sampling and measurement is likely be quite high and should be borne in mind. No health concerns are expected from the PBDE intakes estimated in this study for adults as all had MOEs over 2.5 (EFSA, 2011). The lowest adult MOEs were 2.8 and 3.7 for BDE-99 using a high dust intake rate for household 5 with the high $BDE_{3\text{-}7}$ measurements in their bedroom. Accordingly, estimated infant daily exposures to BDE-99 for the same home have MOEs below those recommended by EFSA for chronic exposure. Using average diet intake data from the 2012 UK TDS with dust exposure data from this study with average dust intake rates we found the lowest MOE estimation to be 2.3 which is similar to the EFSA recommended MOE of 2.5 deemed to indicate a potential health risk. Using high dust intake rates with dust data for this study and 97.5th percentile (P97.5) dietary intake estimates from the 2012 UK TDS this MOE dropped to 0.7 and two additional homes indicated high infant intake MOEs between 2.5 and 3. All other adult and infant MOEs using EFSA reference values and all MOEs using US EPA values were comfortably above the recommended MOE. Follow-up measurement of the PBDE body burdens for infants of parents participating in this study could help describe associations with raised intake estimations.

4 Conclusions

This detailed study is the first anywhere to document concentrations of PBDEs, including BDE-209, in samples of indoor dust and diet with matched human serum and breast milk concentrations. Our findings confirmed that both diet and dust make a contribution to PBDE body burdens and provide new evidence of a wide range in their relative contributions between individuals. Diet appeared to be the primary source of intake of $BDE_{3\text{-}7}$ congeners for the majority of this cohort, and meat consumption demonstrated the strongest significant positive association between diet type and serum $BDEs_{3\text{-}7}$ concentrations. Dust was the cohort's primary source of BDE-209. Rooms containing a carpet or rugs over 20 years old had higher BDE-209 concentrations in their dust. Rooms that were dusted more frequently had less BDE-209, as well as less Penta mix PBDE congeners. Rooms containing sofas or armchairs over 20 years old had higher concentrations of commercial Penta mix PBDE congeners. BDE-209 concentrations in room dusts did not widely correlate with BDE-209 body burdens, possibly due to the congener's relatively large molecular size and low bioaccessibility. Correlations between $BDE_{3\text{-}7}$ congeners in serum and indoor dust were strongest in bedrooms in keeping with the greater proportion of time spent there. Being male and having a lower body fat mass were indicators of higher serum BDE-153 for this cohort. BDE-99 was the congener demonstrating the lowest MOE (and therefore the greatest health risk) and although we found a reduction in dietary exposure to this and other Penta-mix PBDEs since 2002, reducing dietary exposure would still have the greatest effect in reducing body burdens.

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Conflicts of interest: None

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